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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/036,208	10/29/2001	Hiroyuki Odaka	087147-0602	4444

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EXAMINER
ANDERSON, JAMES D

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/036,208	ODAKA ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 25-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 4 and 25-27 ARE PRESENTED FOR EXAMINATION

Applicants' arguments filed 8/20/2007 have been received and entered into the application. No claims amendments were submitted. Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments filed 8/20/2007 have been fully considered but they are not persuasive.

With respect to the 35 U.S.C. 102(a) rejection of claims 4 and 25-27 over WO 98/11884, Applicants argue that "picking and choosing from various compounds of formula I and insulin sensitizers is required to reach an embodiment with the scope of the present claims" (page 2 of Response). This is not found persuasive because WO '884 explicitly teaches combining a compound of Formula I and an insulin-sensitizing agent, including and preferably the claimed pioglitazone, to NIDDM patients to improve their weight and diabetic control (pages 12-13). The instantly claimed sibutramine is exemplified as a preferable compound of the invention disclosed in WO '884 (see Examples). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "When a claim covers several structures or compositions, either

generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art." *Brown v. 3M*, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001). *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. The Board held that the comprehensiveness of the listing did not negate the fact that the compound claimed was specifically taught. The Board compared the facts to the situation in which the compound was found in the Merck Index, saying that "the tenth edition of the Merck Index lists ten thousand compounds. In our view, each and every one of those compounds is described' as that term is used in 35 U.S.C. § 102(a), in that publication."). *Id.* at 1718. See also *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982) (The claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board's finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims). In this case, WO '884 explicitly teaches the use of the instantly claimed sibutramine as well as its combination with insulin sensitizing agents, preferably the claimed pioglitazone. As such, one need not "pick and choose" to arrive at the claimed combination; it is explicitly taught and exemplified in the prior art.

Applicants further argue that the previous Examiner in the parent case held method claims reciting lowering the concentration of glycosylated hemoglobin independent and distinct from methods of treating diabetes, diabetic complications, or IGT. As such, because the PTO held that the present subject matter is not the same as treating diabetes, diabetic complications and IGT, Applicants argue that the present Examiner cannot take a contrary position by

indicating that the claimed lowering of the concentration of glycosylated hemoglobin will naturally result from the methods of WO '884. This argument is not persuasive because, while the MPEP indicates that full faith and credit should be given to the search and action of the previous examiner, if there is a clear error in the previous action or knowledge of other prior art, it is incumbent on the present Examiner to set forth all applicable rejections. In this case, the present Examiner maintains that reducing levels of glycosylated hemoglobin in diabetic patients will naturally result if such patients are administered sibutramine and pioglitazone, regardless of whether or not the prior art recognized that such is the case. If the method steps are the same, *i.e.*, administering sibutramine and pioglitazone to a patient in need thereof, then the results of such administration are an inherent property of those steps. In other words, one cannot separate the therapeutic results of a given treatment regimen if the patient population is the same. Such is the case in the present situation. One skilled in the art would recognize that diabetic patients are in need of reduced glycosylated hemoglobin levels. Accordingly, if a diabetic patient is administered sibutramine and pioglitazone, reduced glycosylated hemoglobin, reduced plasma glucose, reduced plasma insulin, reduced body weight, etc. will naturally result from such administration.

With respect to the 35 U.S.C. 103 rejection of claims 4 and 25-27 over Grossman *et al.* and Hauner in view of WO 93/03724, Applicants argue that they have demonstrated unexpected results per the Declaration of Dr. Odaka filed 3/7/2003. However, the Examiner is not persuaded that unexpected results have been shown because the experimental error in Tables 1 and 2 is so great that a meaningful comparison of the data is not possible. For example, in the Group A controls, the average HbA1 concentration was 0.1% ± 0.5%. Thus, the standard deviation is 5

times greater than the average measured concentration. The standard deviation is also greater than or equal to the measured concentration in the Group B (pioglitazone) (-0.3 ± 0.3%) and Group C (sibutramine) (-0.2 ± 0.5%) animals. If the average % concentration of HbA1 in the Group D (pioglitazone + sibutramine) is -1.2 ± 0.4%, this would indicate that the change from control was from 0.8% to 1.6%. This is well within range that might be expected if the effects of pioglitazone and sibutramine were simply added together considering the high standard deviation present in the results, *i.e.*, -0.6% (pioglitazone) and –0.7% (sibutramine) corresponding to a total of –1.3% on the high end. Compare this to the –1.6% on the high end of the Group D results. Thus, the data presented in the Declaration of Dr. Odaka is not persuasive to overcome the present rejection.

Accordingly, the rejections of record are maintained and reiterated below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 4 and 25-27 are rejected under 35 U.S.C. § 102(a) as being anticipated by WO 98/11884 (prior art of record).

The reference discloses that insulin-sensitizing agents (*e.g.* pioglitazone) can be used in combination with sibutramine to treat diabetes, impaired glucose intolerance and complications of diabetes in which insulin resistance is present (pages 12-13).

The instantly claimed method of reducing glycosylated hemoglobin levels is inherently taught by the reference. When sibutramine and pioglitazone are administered in combination to a patient with diabetes or NIDDM as taught in the reference, a reduction in glycosylated hemoglobin levels is a natural result of such administration.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant claims are drawn to a method of lowering glycosylated hemoglobin levels in mammals through the administration of pioglitazone and sibutramine. The evidence of unexpected results (demonstrated in the 37 C.F.R. 1.132 Declaration of Dr. Okada) has been reconsidered and is not deemed to be sufficient to overcome the prior art (please see discussion *supra*).

Claims 4 and 25-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Grossman *et al.* (Exp. Opin. Invest. Drugs, 1997, vol. 6, pp. 1025-1040) (prior art of record) and Hauner (International Journal of Obesity, 1999, vol. 23, Suppl. 7, pages S12-S17) in view of WO 93/03724 (prior art of record).

Grossman *et al.* review the mechanisms and clinical effects of thiazolidinediones in the treatment of diabetes mellitus. The insulin-sensitizer pioglitazone is disclosed as decreasing hyperglycaemia, hyperlipidaemia, hyperinsulinaemia and glucose intolerance in genetically obese and diabetic yellow KK mice and Zucker fatty rats (p. 1027, left column, first paragraph of Section 3.2). The clinical effects of the thiazolidinedione troglitazone demonstrated a significant decrease in HbA_{1c} supporting the concept that "thiazolidinediones can improve hyperglycaemia

through decreased insulin resistance, as well as favourably influencing lipid metabolism" (p. 1032, second paragraph under Section 5.1.2). It is noted that the instant specification defines glycosylated hemoglobin as "HbA_{1c}" on page 32, line 33. The thiazolidinedione pioglitazone has been shown to reduce mean HbA_{1c} over 12 weeks in two Japanese dose-ranging studies (p. 1034, Table 4 and Figure 1). The reference does not disclose administration of pioglitazone and the anorexiant, sibutramine, in combination to reduce glycosylated hemoglobin.

However, Hauner discloses that the anorexiant sibutramine produced dose-related weight reduction and improved HbA_{1c} levels in randomized clinical trials (page S15).

The motivation to combine the references is found in WO 93/03724 wherein the authors state that, for the treatment of diabetes and disorders related to diabetes, what is needed is "a therapy that may be used in combination with anti-diabetic drugs to treat or prevent obesity, resulting from treatment with an insulin sensitizing drug or an insulin secretion stimulating drug" (p. 5, lines 9-11).

It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed supra). The natural presumption that two individually known antidiabetic agents would, when combined, provide a third composition also useful for treating diabetic conditions,

including reducing HbA_{1c} levels, flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Thus, the present invention of lowering the level of glycosylated hemoglobin (HbA_{1c}) by administering a combination of pioglitazone and sibutramine would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The skilled artisan would reasonably expect that pioglitazone and sibutramine, when combined, would be effective to reduce glycosylated hemoglobin levels because each drug individually has such a therapeutic effect.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

October 31, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER